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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,391	01/08/2002	Eiji Shiojiri	215409US0	9970

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
08/06/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/926,391	SHIOJIRI ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,20-30,33,34,37,38,41 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26-30,33,34,37,38,41 and 42* is/are rejected.

7)☒ Claim(s) *3,20-23 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 3, 20-30, 33, 34, 37, 38, 41 and 42 are pending.

Applicants' amendment and a new Declaration of Eiji Shiojiri and Yoshinobu Takino having a correction to the previously filed Declaration filed May 21, 2007 are acknowledged. Applicant's response and the new Declaration have been fully considered. Claims 3, 20-27, 30, 34 and 38 have been amended, claims 31-32, 35-36 and 39-40 have been cancelled, and a new claim 42 has been added. Therefore, claims 3, 20-30, 33, 34, 37, 38, 41 and 42 are examined.

Withdrawn Claim Objections

2. The previous objection to claim 24 is withdrawn in view of applicant's amendment to the claim, and applicants' response at page 14 in the amendment filed May 21, 2007.

Withdrawn Claim Rejections - 35 USC § 112

3. The previous rejection of claims 25, 31-32, 35-36 and 39-40, under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in view of applicants' amendment to the claim, and applicants' cancellation of the claims in the amendment filed May 21, 2007.

Withdrawn Claim Rejections - 35 USC § 102

4. The previous rejection of claims 24-26, 38 and 41 under 35 U.S.C. 102(b) as being anticipated by Janecka *et al.* (J. Med. Chem. 38, 2922-2924 (1995)), is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 13-14 in the amendment filed May 21, 2007.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 24, 26-30, 33, 34, 37, 38, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (1); a melanocyte-stimulating hormone inhibitory composition, a cosmetic or external preparation for the skin, or a whitening agent comprising the compound of formula (1); and a method of suppressing pigmentation of skin in a mammal by topically administering to the mammal the compound of formula (1), wherein Ar in the compound of formula (1) is an unsubstituted naphthyl group, does not reasonably provide enablement for the compounds of formula (1); a melanocyte-stimulating hormone inhibitory composition, a cosmetic or external preparation for the skin, or a whitening agent comprising the compound of formula (1); and a method of whitening in a subject by administering an agent comprising a compound of Formula (1), where wherein Ar in the compound of formula (1) is a substituted naphthyl group, but the substituent is not defined, and the activity of the compound is not specified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 24, 26-30, 33, 34, 37, 38, 41 and 42 encompass a compound of formula (1) (claim 24); a melanocyte-stimulating hormone inhibitory composition (claims 26-29), a cosmetic or external preparation for the skin (claims 33, 37, 41) or a whitening agent (claim 38) comprising the compound of formula (1); and a method of whitening (claims 30, 34, 42) in a subject by administering an agent comprising the compound of Formula (1). The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the

present invention provides di- or tri-peptide derivatives with the Formula (1) having a naphthyl group, which can inhibit the action of melanocyte-stimulating hormone, thereby the compound can be used as an active ingredient in a melanocyte-stimulating hormone inhibitory composition, a whitening agent, an immunofunction controlling agent, an appetite controlling agent, or a cosmetic preparation (pages 3-6). There are no indicia that the present application enables the full scope in view of a compound of Formula (1) and a method of whitening in a subject by administering an agent comprising the compound of Formula (1) as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the compounds of Formula (I) having an undefined substituent on the naphthyl group and their effects in inhibiting melanocyte-stimulating hormone and in whitening in a subject, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification merely discloses that specific compounds of Formula (1) having an unsubstituted naphthyl group such as D-1-Nal-Arg-LeuNH_2, D-2-Nal-Arg-LeuNH_2, L-1-Nal-

Arg-LeuNH$_2$, and L-2-Nal-Arg-LeuNH$_2$ have inhibitory activity against MSH (test Example 1), suppress the melanin formation (test Example 2), and suppress pigmentation in brown guinea pig model (test Example 4). However, there are no working examples indicating the use of compounds of Formula (1) having a substituted naphthyl group in inhibiting melanocyte-stimulating hormone and in whitening in a subject for in vivo treatment.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., references shown in pages 2-3 of the specification) indicates the use of MSH inhibitors have a pigmentation inhibitory activity. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on the identities of various compounds of formula (1) with a substituted naphthyl group that are effective in inhibiting melanocyte-stimulating hormone and in whitening in a subject to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a compound of formula (1) having a substituted naphthyl group and a method of whitening in a subject by administering the compound of Formula (1), however, the specification has not shown the use of any compound of Formula (1) having a substituted naphthyl group, thus the identities of active compounds of Formula (1) with a substituted naphthyl group and their in vivo effects are not adequately described in the specification, the invention is unpredictable regarding the structures of the compounds of Formula (1) having a substituted naphthyl group that are effective in the treatment.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a compound of formula (1) having a substituted or unsubstituted naphthyl group and a method of whitening in a subject by administering an agent comprising the compound of Formula (1). While the specification discloses specific compounds of Formula (1) such as D-1-Nal-Arg-LeuNH$_2$, D-2-Nal-Arg-LeuNH$_2$, L-1-Nal-Arg-LeuNH$_2$, and L-2-Nal-Arg-LeuNH$_2$ have inhibitory activity against MSH (test Example 1), suppress the melanin formation (test Example 2), and suppress pigmentation in brown guinea pig model (test Example 4), the specification does not describe the use of various compounds of Formula (1) having a substituted naphthyl group in whitening in a subject, nor indicates how to extrapolate the in vitro effect to in vivo treatment. Furthermore, there are no working examples indicating the compounds of Formula (1) with different substituents on naphthtyl group have inhibitory activity against MSH and the use of these compounds in whitening either in vitro or in vivo treatment. Since the specification does not provide sufficient teachings on the identities of various compounds of Formula (1) having a substituted naphthyl group that are effective in whitening in a subject, it is necessary to carry out undue experimentation to identify the compounds of Formula (1) having a substituted naphthyl group that are effective for in vivo treatment.

(6). Nature of the Invention

The scope of the claims encompasses a compound of formula (1) having a substituted naphthyl group in a subject by administering an agent comprising the compound of Formula (1), but the specification does not provide sufficient teachings on the identities of active compound of Formula (1) having a substituted naphthyl group and their effects either in vitro or in vivo treatment. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the claimed compounds and methods associated with the variants, the structures of active compound of Formula (1) having a substituted naphthyl group are unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify the compounds of Formula (1) having a substituted naphthyl group that are active in the treatment.

Response to Arguments

Applicants indicate claim 24 has been amended to specifically define R^7, R^4, X^1, X^2, X^3 and R^9, and further Ar is disclosed concretely at page 10, lines 15-24 of the specification, with respect to Claims 30, 34 (a method of whitening) and Claim 38 (a whitening agent), Applicants have limited the scope of these claims to define the whitening agent has exhibiting inhibition of pigmentation by ultraviolet rays (See Test Example 4 and at page 18, line 17 to 22 of the specification), thus the skilled artisan would readily appreciate how to prepare substituted naphthyl compounds and how to practice the claimed method without undue experimentation. In view of the amendments coupled with the description provided in the specification, and further supported by the Declaration of Shiojiri and Takino, the skilled artisan would be fully enabled to make and use the full scope of claimed compounds (pages 11-13 of the response).

Applicant's response and the Declaration of Shiojiri and Takino have been fully considered, however, the arguments are not found persuasive because of the following reasons. In the Declaration of Shiojiri and Takino, additional 16 compounds have been presented. However, compounds **8-16** are not within the scope of the claimed invention since they do not contain "naphthyl" group, only compounds **1-7** are within the scope of compounds of Formula

(1). Among these 7 compounds, compound **1-5** and **7** (i.e., Nal-Arg-Leu tripeptides with three different acyl group in Y, Nal-Lys-Leu, and Nal-Lys-Trp tripeptides) are tripeptides with unsubstituted naphthyl group. While the specification discloses the hydrogen in Ar group may be replaced by one or more halogen, alkyl group having 1 to 6 carbon atoms, hydroxyl group, hydroxyalkyl group having 1 to 6 carbon atoms, nitro group, alkoxy group having 1 to 6 carbon atoms , carboxyl group or sulfonic acid (page 10, lines 15-23), compounds of formula (1) in claim 24 encompass a tripeptide with an undefined substituent on the naphthyl group. Since neither the specification nor the Declaration of Shiojiri and Takino provides adequate information regarding the use of the compound of formula (1) with a substituent on the naphthyl group in inhibiting MSH and/or whitening in a subject, it requires undue experimentation to identify a compound of Formula (1) having a substituted naphthyl group that is effective for in vivo treatment. Therefore, the full scope of the claims is not enabled.

Claim Objections

6. Claims 3, 20-23 and 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

7. Claims 24, 26-30, 33, 34, 37, 38, 41 and 42 are rejected, and claims 3, 20-23 and 25 are objected to.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.

Primary Patent Examiner

CHIH-MIN KAM
PRIMARY EXAMINER

CMK

July 31, 2007